REMARKS

Claims 1-20 were pending in the application. Upon entry of these amendments, Claims 1-20 will be pending and under active consideration. Claims 1 and 14 are independent.

Applicants respectfully request entry of the amendments and remarks made herein into the file history of the present invention. Reconsideration and withdrawal of the rejections set forth in the above-identified Office Action are respectfully requested.

I. The Rejections Under 35 U.S.C. § 102(b) Should Be Withdrawn

The Office Action, at pages 2-5, rejects Claims 1-20 as allegedly being anticipated by Sargiacomo *et al.* (*J. Hepat.*, 28:480-490, 1998)(hereinafter, "Sargiacomo"), as further evidenced by Haruna *et al.* (*Hepatology*, 23:476-481, 1996)(hereinafter, "Haruna"), under 35 U.S.C. § 102(b). The Office Action alleges that Sargiacomo teaches that cell preparations from intact fetal livers were seeded into polystyrene flasks and cultured. The Office Action alleges further that, since the fetal liver cell preparations taught in Sargiacomo are disclosed to be isolated from human fetal livers, as are the presently-claimed isolated and identified hepatic progenitor cells, the cell preparations of Sargiacomo will have inherently the same physical and biochemical properties as the presently-claimed isolated and identified hepatic progenitor cells. The Office Action draws the alleged conclusion, therefore, that Sargiacomo teaches the isolation and identification of bipotent liver progenitor cells isolated from fetal livers. Applicants traverse respectfully.

Applicants submit respectfully that Claims 1-20, as amended, are not anticipated by Sargiacomo because Sargiacomo does not disclose each and every element of those amended

claims, either explicitly or inherently, as is required for a *prima facie* showing of anticipation under 35 U.S.C. § 102(b). In particular, Claim 1, as amended, is directed to a composition comprising isolated **single-cell** bipotent hepatic progenitors which express at least one intercellular adhesion molecule (ICAM) antigen and do not express major histocompability complex (MHC) class Ia antigen, in which the bipotent hepatic progenitors **have a capacity to differentiate when exposed to differentiation-inducing growth conditions**. Despite the Office Action's allegation that Sargiacomo teaches the isolation and identification of bipotent liver progenitor cells isolated from fetal livers, Applicants again respectfully submit that Sargiacomo does not teach or suggest isolated single-cell hepatic progenitors, nor does Sargiacomo teach or suggest the identification of liver progenitors capable of differentiation when exposed to differentiation-inducing growth conditions. Further, Applicants submit respectfully that the teachings of Haruna do not evidence Applicants' claimed inventions, nor would Haruna cure the deficiencies of Sargiacomo in teaching or suggesting the single-cell bipotent hepatic progenitors capable of differentiation when exposed to differentiation-inducing growth conditions as presently claimed.

Applicants respectfully submit that Sargiacomo teaches a fetal liver culture system which allows morphogenetic interactions consistent with the development of hepatic function. Fundamental to Sargiacomo's method is that intact "multi-size spherical hepatic units" were seeded into culture medium, to begin the growth process, so that hepatic architecture would be present. The importance of the integrity of these hepatic units to the Sargiacomo method is indicated in the sentence bridging pages 483-484, which recites that "[A]ll the hepatic specimens used for preparing the human FLCC [Fetal Liver Cell Culture] were immediately checked for structural integrity by LM [Light Microscope]. Even more significant is the fact that Sargiacomo

teaches at pages 480-481 that the use of intact, 3-dimensional cell clusters is a cure to deficiencies noted in the art of maintaining isolated hepatocytes in cell culture where the method includes "dissociation of cells from the tissue matrix in which reciprocal interactions are critical for the maintenance of a differentiated cellular state" (sentence bridging pages 480-481). Accordingly, and while not acquiescing in the argument that the cell clusters of Sargiacomo contain bipotent hepatic progenitors, Applicants submit respectfully that Sargiacomo not only fails to teach the isolation of single-cell bipotent hepatic progenitors, but Sargiacomo actually teaches away from single-cell culture methods.

Further, Applicants again respectfully submit that Sargiacomo does not even indicate that bipotent hepatic progenitors exist within the cell cultures taught by Sargiacomo. Inasmuch as Sargiacomo begins cell culture with intact hepatic units (**i.e., not the single-cell bipotent hepatic progenitors of the presently claimed invention**), it seems likely that differentiated hepatocytes and biliary cell clusters were present in the initial cell culture. As Sargiacomo performed none of the tests taught by Applicants to identify the presence of bipotent hepatic progenitors in Sargiacomo's cell cultures, there is no way to know whether such progenitors are actually present. The Office Action indicates that Haruna teaches that hepatic progenitors are present in fetal human liver, with the implication that the cells identified by Haruna would be present in Sargiacomo's cell culture. Without acquiescing in the allegation that Haruna's methods actually identify bipotent hepatic progenitors, Applicants submit respectfully that Haruna teaches immunoperoxidase staining of formalin-fixed paraffin sections of ***intact*** liver, not dissociated liver components as taught by Sargiacomo. Hence, Applicants again respectfully submit that one cannot determine whether the cells identified by Haruna are present in the Sargiacomo cell preparation.

Furthermore, Applicants respectfully submit that application of the Haruna identification methods to the cultures of Sargiacomo would not yield the isolated single cell bipotent hepatic progenitor cells of the present invention having the ***capacity to differentiate when exposed to differentiation-inducing growth conditions***. Applicants' submit respectfully that, as one skilled in the art will no doubt immediately recognize, mammalian liver cells that have been subjected to formalin fixation, and that are subsequently contained within peroxidase-stained paraffin sections, are no longer viable. Hence, such cells are not capable of differentiation as required under Claims 1 and 14, as amended.

Applicant submits respectfully that the claims of the present invention, as amended, are not anticipated by Sargiacomo, which does not teach or suggest each and every element of the present claims, and that the rejection to Claims 1-20 under 35 U.S.C. § 102(b) has been overcome. Accordingly, Applicant requests respectfully that the rejection to Claims 1-20 under 35 U.S.C. § 102(b) be withdrawn.

II. Rejections Under 35 U.S.C. § 112, Second Paragraph

At page 2 of the Office Action, Claims 1 and 14 are rejected under 35 U.S.C. § 112, second paragraph, as allegedly being indefinite for failing to point out particularly and claim distinctly the subject matter regarded as the invention.

In particular, at page 2 of the Office Action, the Office Action contends that Claims 1 and 14 are vague and indefinite in that the claims recite that the composition comprises isolated *single-cell* bipotent hepatic progenitors. The Examiner is of the opinion that it is unclear what the term "single-cell" encompasses and the specification fails to provide a definition for the term.

The Examiner contends that the term could mean a single bipotent hepatic progenitor cell in a composition of other cells. Applicants traverse respectfully.

Without acquiescing in the propriety of the rejection, Applicants respectfully point out to the Examiner that the specification more than adequately defines what is meant by the term single cell. For example, Applicants respectfully direct Examiner's attention to page 28, lines 20-21 of the specification which teaches the preparation of a single-cell suspension for isolating human hepatic precursors. In particular, the specification recites at page 14, lines 8-10 that single cell suspensions are obtained by incubating the livers with 0.05% trypsin and 0.5mM EDTA or 10units/ml thermolysin (Sigma, St. Louis, MO) and 100units/ml deoxyribonuclease I (Sigma) for at 37°C. Thus, Applicants submit respectfully that Claims 1 and 14 are not unclear, and Applicants request respectfully that the 35 U.S.C. § 112, second paragraph, rejection of Claims 1 and 14 be withdrawn.

CONCLUSION

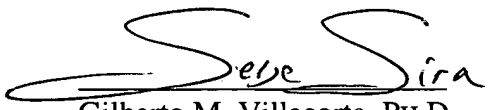
Applicants submit that the application is in condition for allowance. Favorable reconsideration, withdrawal of the rejections set forth in the above-noted Office Action, and an early Notice of Allowance are requested.

Applicants' undersigned attorney may be reached in our Washington, D.C. office by telephone at (202) 625-3500. All correspondence should be directed to our address given below.

AUTHORIZATION

Applicants believe there is no fee due in connection with this filing. However, to the extent required, the Commissioner is hereby authorized to charge any fees due in connection with this filing to Deposit Account 50-1710 or credit any overpayment to same.

Respectfully submitted,



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